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Stationary-Mixing Field-Programmable Pin-Constrained Digital Microfluidic Biochip

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ABSTRACT

This paper introduces a Field Programmable Pin-Constrained (FPPC) architecture for a Digital Microfluidic Biochip (DMFB) that integrates a new stationary hydrodynamic mixing technology. Compared to the traditional rotation-based mixing, stationary mixing is faster, requires fewer electrodes, and limits residue production and the likelihood of biofouling. Although the stationary mixing principle has been established, programmable DMFB architectures that feature stationary mixing have not been investigated or evaluated. Simulation results show that the Stationary Mixing FPPC (SM-FPPC) architecture introduced here outperforms existing Direct Addressing (DA) and FPPC DMFBs that employ traditional rotation-based mixing. An analysis based on a commercially available Printed Circuit Board (PCB) cost calculator demonstrates a 31% reduction in cost compared to the lowest cost PCB reported in prior literature.

1. Introduction

Laboratory-on-a-chip (LoC) technology integrates one or more benchtop-scale laboratory procedures into a single micro-scale chip, reducing both time and cost through miniaturization and automation. Among the competing LoC technologies, Digital Microfluidic Biochips (DMFBs) [1–6], based on the principle of electrowetting [7], offer the additional benefits of programmability and scalable low-cost fabrication based on traditional Printed Circuit Board (PCB) manufacturing technology. Successful DMFB demonstrations have been reported for biochemical applications including DNA amplification [8], air/water pollution monitoring [9], analysis of bacterial resistance to antibiotics [10], epigenetics [11], cellular genetic engineering [12], and wine tasting [13], among many others. As a result, there is great interest in developing techniques to improve the performance and reduce the cost of DMFBs in practice.

Fluid transport and mixing are two of the most fundamental capabilities that virtually all LoCs are capable of performing. Historically, DMFBs perform mixing by merging two liquid droplets (via transport) and then physically moving the merged droplet back and forth [1], which is effectively a transport operation, although often restricted to a relatively small sub-region of the device. One of the drawbacks of rotation-based mixing—which has historically lacked an alternative short of switching to another LoC technology—is that certain biological samples, such as proteins, have a tendency to absorb onto the chip surface; as a result, repeated transport of droplets containing such samples leads to biofouling, cross-contamination, and, eventually, physical degradation of the underlying substrate [14].

Recently, stationary hydrodynamic mixing has been introduced as an alternative to rotation-based mixing [14]. The basic principle is to hold a droplet in place and to generate flow circulation by applying a high frequency AC voltage to the droplet. This induces internal circulation within the droplet, leading to faster mixing times than traditional rotation-based mixing, and eliminates the drawbacks listed above. The impact of stationary mixing on bioassay execution time has not yet been quantified, either through experimentation or simulation. Likewise, fully integrated DMFB architectures that perform stationary mixing have not yet been proposed or evaluated.

In response, this paper introduces a Stationary Mixing Field-Programmable Pin-Constrained (SM-FPPC) DMFB and its compiler. The compilation process is similar to that of an earlier FPPC DMFB design that features rotation-based mixing [15], but includes a few subtle differences. We estimate the cost of Printed Circuit Boards (PCBs) for two SM-FPPC variants, and show that the cheaper variant costs 31% less than the lowest cost PCB for a traditional FPPC DMFB. Through simulation, we show than the SM-FPPC runs faster than both Direct Addressing and FPPC DMFBs of comparable size, due to faster mixing times and slightly shorter droplet routes. As stationary mixing can be accomplished using a 1×3 electrode configuration, more and faster concurrent mixing operations can be performed on a fixed-size device when compared to traditional rotation-based mixing.

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2. Background

The basic principle underlying digital microfluidics is the electrowetting effect [7], depicted below in Fig. 1: applying a voltage to a droplet changes its shape: the contact angle with the surface flattens, and a greater portion of the droplet comes into contact with the surface, effectively "wetting" it.

As shown in Fig. 2(a), a DMFB is a 2D array of patterned electrodes separated from fluid by an insulating hydrophobic layer [1–6]. In Fig. 2(b) An optional top plate may contain a ground electrode, which can assist with droplet movement. Droplets in the system must be slightly wider than an electrode in order to induce movement.

Fig. 3 depicts the basic principles underlying droplet movement in a DMFB. Activating control electrode CE2 underneath the droplet holds it in place (left). It is important to observe that the droplet length is greater than the length of CE2, and it extends into the physical space above control electrodes CE1 and CE3 as well. Activating CE3 in addition to CE2 creates a horizontal force that centers the droplet between the two electrodes (middle); this force can only be induced because a portion of the droplet in its initial position is directly on top of CE3. Lastly, deactivating CE2, while leaving CE3 activated, releases the portion of the force that hold the droplet between CE2 and CE3, allowing the droplet to fully position itself on top of CE3 (right).

Droplet motion induced by electrode activation and deactivation provides a DMFB with an instruction set architecture (ISA) containing five instructions, as shown in Fig. 4: Transport, Split, Merge, Mix, Store. As the DMFB itself is a spatially parallel array consisting of a uniform set of electrodes, each of these operations can be performed anywhere on the surface of the chip; thus, the DMFB is "reconfigurable" [16].

In addition to the five reconfigurable operations, a DMFB typically supports several non-reconfigurable operations as well. For example, input and output (including waste production) use reservoirs that are physically placed on the perimeter of the chip; the locations and roles of the reservoirs do not change when the DMFB is in use, so they are not reconfigurable. External devices such as sensors, mixers, and heaters may be placed at any location on the chip surface [17–31]; such locations can still perform the five basic operations, but are now enhanced with additional capabilities. Similarly, specialized electrodes can be fabricated to perform operations such as electroporation [12] or non-uniform splitting [32].

3. Rotation-based and stationary mixing

Historically, DMFBs have performed mixing by sectioning off a rectangular sub-array of the chip (1×4, 2×2, etc.); we refer to these as rotation-based mixers. Prior work has shown that the size of the sub-array and the path that the droplet travels through the sub-array impact mixing time [15]. In general, larger mixers yield shorter mixing time, but consume more spatial on-chip area, thereby reducing the amount of available parallelism; this creates a tradeoff that must be properly evaluated when determining how to best map a bioassay onto a DMFB for high-throughput execution [33–35].

Recently, stationary mixing, in which an AC activation voltage is applied to an otherwise stationary droplet, has emerged as an alternative to rotation-based mixing [14]. If the voltage is applied by inserting a wire directly into the droplet, as shown in Fig. 5(a), the regions with the highest intensity electric fields heat up, resulting in a temperature gradient that alters the permittivity and conductivity of the droplet, inducing a gradient of properties throughout the droplet. This, in turn, creates an electrohydrodynamic effect that generates circulating motion; in general, liquids with higher conductivity require higher frequencies to induce this effect.

A slightly different approach is required to induce stationary mixing using a DMFB, i.e., 2D array of patterned electrodes, which does not include a mechanism to insert a wire directly into the droplet. To induce stationary mixing in a DMFB, as shown in Fig. 5(b), adjacent 1.5 mm × 1.5 mm electrodes separated by ~30 μm are actuated with applied voltages of opposite polarities. In Fig. 5(c) and (d), the same principle can be applied to a DMFB that features a closed top plate with a single electrode; activating the top plate in conjunction with the patterned electrodes at the bottom generates a stronger electric field gradient within the droplet, leading to faster mixing.

Stationary mixers offer faster mixing times that traditional rotation-based mixers while consuming less on-chip area. Ref. [15] reported a ~10 s mixing time for a 2×2 rotation-based mixer, compared to ~6 s for a 3×2 rotation-based mixer and ~3 s for a 4×2 rotation-based mixer. In contrast, Ref. [14] reports stationary mixing times of less than 1 s, depending on the AC voltage applied and the actuation frequency.

The performance of stationary mixing depends on several parameters, which Ref. [14] discussed in great detail. In general, increasing the frequency and/or amplitude of the applied AC voltage reduced the mixing time, up to a threshold; beyond the threshold, the droplet undergoing stationary mixing shed pico-liter "satellite" droplets, thereby reducing volume (and potentially contaminating other droplets nearby). Mixing efficiency was shown to improve when the gap between top and bottom plates increased, with benefits saturating at ~350 μm. The introduction of salts and DNA to the samples decreased electrothermal effects, which could be compensated by increasing the frequency of the applied AC voltage; using a thermal imaging camera, it was shown that doing this induced a negligible increase in droplet temperature. Typical operating parameters based on the experiments reported in Ref. [14] were to apply a 100 V root-mean-squared (RMS) AC voltage at 1 kHz using a sine waveform.

4. Stationary Mixing Field-Programmable Pin-Constrained DMFB

This section desires a low-cost programmable DMFB architecture that can integrate stationary mixing; here, we restrict our discussion to standard electronic Printed Circuit Board (PCB) fabrication. Prior work has shown that the foremost cost-drivers for PCB-based DMFBs are the number of PCB layers, followed by the number of control pins [36]. The most expensive DMFBs are typically those that employ direct addressing, i.e., each control pin drives exactly one electrode; the number of PCB layers is determined by an escape route, which connects each internal electrode to a control pin on the perimeter of the chip [37,38]. The quality of the escape routing algorithm can significantly impact the number of PCB layers required.

Pin-sharing [39] allows one control pin to drive several electrodes, which reduces the total number of signals that must be delivered to the PCB, thereby reducing cost. Overly aggressive pin-sharing can be detrimental to PCB escape routing when a single wire must connect electrodes across the entire 2D span of the chip, creating blockages that push other

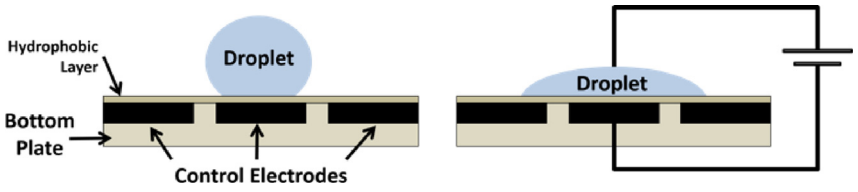

Fig. 1. Illustration of the electrowetting effect.